

In the Claims:

Please cancel claims 1 - 47 without prejudice.

Please add new claims 48 - 81 as follows:

48. (New) A method of cloning a viable animal by nuclear transfer, wherein the method is capable of introducing one or more stable genetic modifications into the cloned animal, the method comprising the steps of:

- Q
- (a) obtaining a tissue sample comprising a population of NENS somatic cells as a source of nuclear donor material;
  - (b) culturing the population of cells through a plurality of passages so that a sufficient number of cell doublings occur to permit the introduction of controlled genetic modifications into the cells and confirmation of the propagation of the genetic modifications through subsequent culturing passes;
  - (c) inserting a cell from the population, or a nucleus isolated from the cell, into an enucleated oocyte to form a cybrid;
  - (d) activating the cybrid;
  - (e) culturing the activated cybrid until greater than a 2-cell developmental stage;
  - (f) transferring the activated cybrid into an appropriate host such that the activated cybrid develops into a fetus; and
  - (g) maintaining the fetus in the host until the fetus is capable of surviving and maturing into a viable animal outside of said host.

49. (New) The method of claim 48, wherein cells from the population of cells undergo 10 or more cell doublings.

50. (New) The method of claim 48, wherein cells from the population of cells undergo 20 or more cell doublings.

51. (New) The method of claim 48, wherein the method further includes the steps of selecting a subpopulation of cells from the population of somatic cells and subjecting the subpopulation of cells to further culturing passes.

52. (New) The method of claim 50, wherein cells from the subpopulation of cells are subject to genetic modification to produce transformed cells.

53. (New) An animal made by the method of claim 48.

54. (New) A transgenic animal made by the method of claim 51.

Q' 55. (New) An organ or tissue obtained from an animal made by the method of claim 48.

56. (New) An embryo made by the method of claim 48.

57. (New) A fetus made by the method of claim 48.

58. (New) A cell line derived from cells obtained from an animal made by the method of claim 48.

59. (New) A method for cloning a mammal with a cloning efficiency of better than ten percent (10%), said method comprising the steps of:

(a) inserting a somatic cell, or nucleus isolated from the somatic cell, derived from a somatic cell culture having undergone a plurality of culturing passages so that a sufficient number of cell doublings has occurred to permit the introduction of controlled genetic modifications into the cells and confirmation of the propagation of the genetic modifications through subsequent culturing passages, into an enucleated oocyte to form a cybrid;

(b) activating the cybrid;

(c) culturing the activated cybrid until greater than a 2-cell developmental stage;

(d) transferring the activated cybrid of step (c) into an appropriate host such that the activated cybrid develops into a fetus;

(e) maintaining the fetus in the host until the fetus is capable of surviving and maturing into a viable animal outside of the host;

wherein the cloning efficiency of such method is better than ten percent (10%).

60. (New) A method for the cloning of a male mammal, said method comprising the steps of:

ai (a) inserting a male somatic cell, or nucleus isolated from the somatic cell, selected from a somatic cell culture having undergone a plurality of culturing passages so that a sufficient number of cell doublings has occurred to permit the introduction of controlled genetic modifications into the cells and confirmation of the propagation of the genetic modifications through subsequent culturing passages, into an enucleated oocyte to form a cybrid;

(b) activating the cybrid;

(c) culturing the activated cybrid until greater than a 2-cell developmental stage;

(d) transferring the activated cybrid of step (c) into an appropriate host such that the activated cybrid develops into a fetus;

(e) maintaining the fetus in the host until the fetus is capable of surviving as a viable animal outside of said host.

61. (New) The method of claim 60, wherein the male somatic cell is a male NENS somatic cell.

62. (New) The method of claim 60, wherein the male somatic cell derives from a somatic cell culture wherein cells in the culture have undergone 20 or more cell doublings.

63. (New) A method for improving blastocyst development rates from cybrids produced by nuclear transfer from a donor cell to an enucleated oocyte, said method comprising the steps of:

(a) activating the enucleated oocyte with an inhibitor selected from the group consisting of: protein kinase inhibitor and a protein synthesis inhibitor, prior to, during or after fusion with the donor cell nucleus; and

(b) electrostimulating the cybrid prior to, during or after fusion.

64. (New) A method for producing an animal clone with genetically-engineered targeted genetic alterations, said method comprising the steps of:

Q (a) altering in a targeted manner the nuclear DNA of somatic cells to produce transformed cells;

(b) culturing the transformed cells through a plurality of culturing passages so that a sufficient number of cell doublings has occurred to permit the introduction of controlled genetic modifications into the cells and confirmation of the propagation of the genetic modifications through subsequent culturing passages;

(c) inserting nuclear material from the transformed cells into an enucleate oocyte to form a cybrid;

(d) activating the cybrid;

(e) culturing the activated cybrid until greater than a 2-cell developmental stage to form an embryo;

(f) transferring the embryo into an appropriate host such that the embryo develops into a fetus; and

(g) maintaining said fetus in said host until said fetus is capable of surviving and maturing into a viable animal outside of said host.

65. (New) An transgenic animal made by the method of claim 64.

66. (New) An organ or tissue obtained from an animal made by the method of claim 64.

67. (New) An embryo made by the method of claim 64.

68. (New) A fetus made by the method of claim 64.

69. (New) A cell line derived from cells obtained from an animal made by the method of claim 64.

70. (New) An improved method of cloning a mammal by nuclear transfer comprising:

Q' (a) the introduction of a donor cell from the mammal, or donor cell nucleus, into an enucleated oocyte of the same species as the donor cell to form a cybrid;

(b) inserting the cybrid into the uterus of a host mother of said species so as to cause implantation of the cybrid into the uterus to form a fetus, and permitting the fetus to develop into the cloned mammal,

wherein the improvement comprises using as the donor cell, or donor cell nucleus, a somatic cell that has been cultured through a plurality of culturing passages so that a sufficient number of cell doublings has occurred to permit the introduction of controlled genetic modifications into the donor cells and confirmation of the propagation of the genetic modifications through subsequent culturing passages, and wherein the donor cell, or donor cell nucleus, has been genetically transformed to comprise at least one addition, substitution or deletion of a nucleic acid or nucleic acid sequence.

71. (New) An animal made by the method of claim 69.

72. (New) An organ or tissue obtained from an animal made by the method of claim 69.

73. (New) An embryo made by the method of claim 69.

74. (New) A fetus made by the method of claim 69.

75. (New) A cell line derived from cells obtained from an animal made by the method of claim 69.

76. (New) A process by which genetically-altered and non-genetically altered animals may be produced, such process comprising the steps of:

- Q1
- (a) isolating a diploid donor cell;
  - (b) culturing the diploid donor cell for more than about 20 cell doublings;
  - (c) optionally altering in a targeted manner the genome of one or more cells of the diploid donor cells to create transformed donor cells;
  - (d) optionally screening and selecting from the cells stable transformed cells;
  - (e) reconstituting an embryo employing nuclei transfer techniques using nuclei from the cells of step (b), or optionally steps (c) or (d);
  - (f) culturing the embryo *in vivo* or *in vitro* to a blastocyst;
  - (g) optionally screening and selecting from the blastocysts stable transformed blastocysts;
  - (h) transfer of one or more the blastocysts of steps (f) or (g) to medium capable of allowing the one or more blastocysts to develop into a viable animal.

77. (New) An animal made by the method of claim 75.

78. (New) An organ or tissue obtained from an animal made by the method of claim 75.

79. (New) An embryo made by the method of claim 75.

80. (New) A fetus made by the method of claim 75.

81. (New) A cell line derived from cells obtained from an animal made by the method of claim 75.